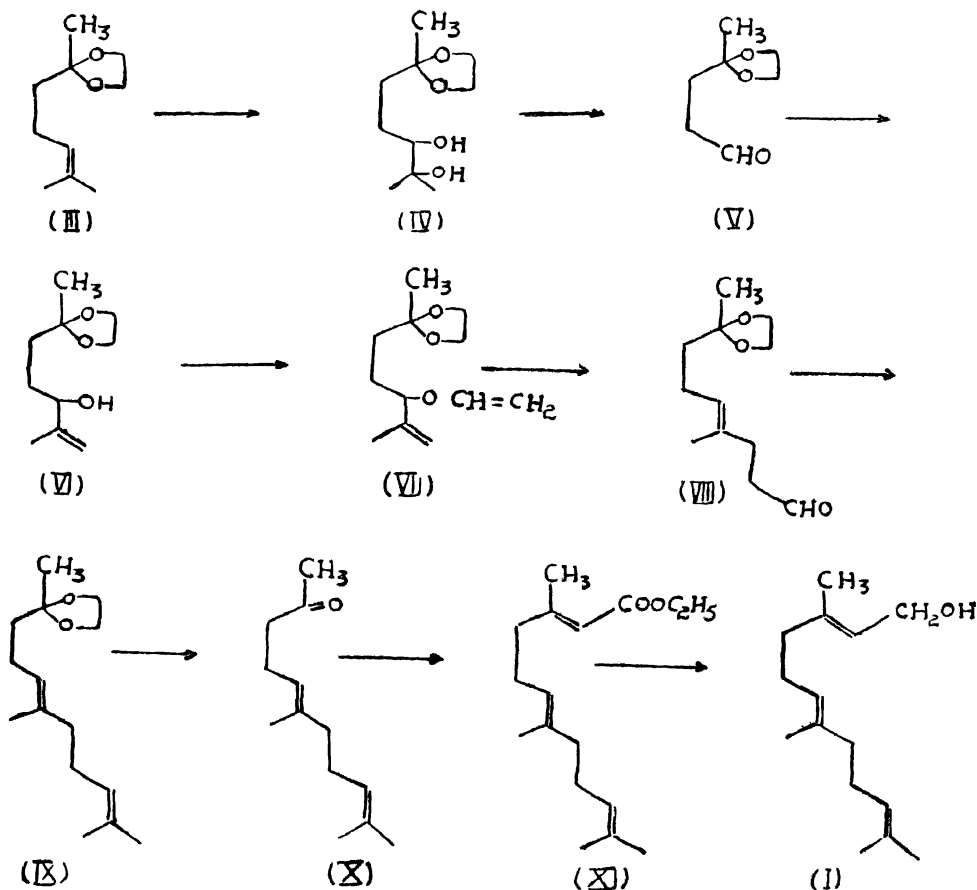


Terpenoids: Part. XLI. Syntheses of *trans*-2, 6-Farnesol and *trans*-Nerolidol.

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Starting from *trans*-geranylacetone, obtained through the Claisen rearrangement of properly substituted vinyl ether followed by Wittig reaction with isopropyltriphenylphosphonium iodide and deketalation, new syntheses of *trans*-2,6-farnesol and *trans*-nerolidol have been accomplished.

Farnesol, a sesquiterpenoid primary alcohol, was isolated from *Abelmoschus moschatus* Moensch¹ and from other essential oils². It has also been prepared commercially by isomerising the *trans*-nerolidol³.



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On the basis of physical and chemical properties⁴ and syntheses^{5,6} its structure has been well established as (I). It can exist in four different isomeric forms i.e., *trans-trans*, *cis-trans*, *cis-cis* and *trans-cis* and a stereoselective synthesis of *trans*, *trans*-farnesol has recently been reported by Corey and coworkers⁷.

The present studies report a new synthesis of *trans*, *trans*-farnesol, contaminated with traces of its *cis*, *trans*-isomer through the sequence of reactions as outlined above.

2-Methyl-6 : 6-ethylenedioxy-heptan-2,3-diol (IV), the starting material, was procured in 29 per cent yield by the neutral potassium permanganate oxidation⁸ of 2-methyl-6 : 6-ethylenedioxy-2-heptene (III) which was further oxidised with lead tetraacetate⁹ in dry benzene to 4 : 4-ethylenedioxy-pentanal (V) in 67 per cent yield. The aldehyde was submitted to Grignard reaction with isopropenyl-magnesium bromide in tetrahydrofuran to afford 2-methyl-6 : 6-ethylenedioxy-1-hepten-3-ol (VI) in 59 per cent yield. The allylic carbinol (VI) was transformed into its vinyl ether (VII) by freshly-crystallised mercuric acetate catalysed *trans*-etherification¹⁰ with ethyl-vinyl ether. The purified 2-methyl-6 : 6-ethylenedioxy-1-hepten-3-vinyl ether (VII) on Claisen rearrangement¹¹, under nitrogen, in a sealed tube provided 4-methyl-8 : 8-ethylenedioxy-*trans*-4-nonen-1-al (VIII) in 85 per cent yield. The *trans* nature of the double bond in the aldehyde (VIII) is supported by the N.M.R. spectrum of the synthesised farnesol (I) which exhibited signals at τ 8.34 and 8.41 with relative intensities of 1 : 2 respectively¹².

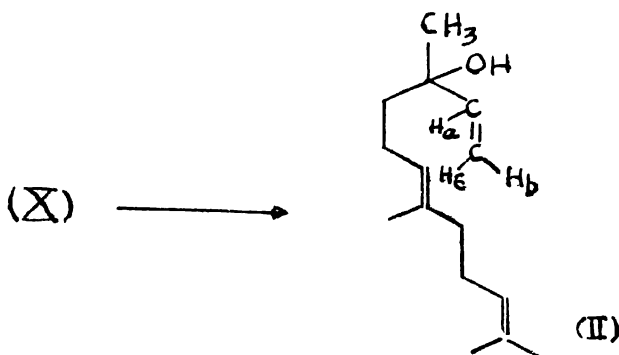
The aldehyde (VIII) was subjected to Wittig reaction¹³ with isopropyltriphenylphosphonium iodide in dimethyl sulphoxide in the presence of sodium hydride, when it gave 2,6-dimethyl-10 : 10-ethylenedioxy-*trans*-2,6-undecadiene (IX) in 79 per cent yield. The ketal (IX) was deketalised with *p*-toluenesulphonic acid in aqueous acetone solution under mild conditions to furnish, in 80 per cent yield, 6,10-dimethyl-*trans*-5,9-undecadien-2-one (X). The latter was characterised through its 2,4-dinitrophenylhydrazone and semicarbazone derivatives. The ketone (X) was submitted to the modified Wittig reaction¹⁴ with ethyl diethylphosphonoacetate in the presence of sodium hydride using 1,2-dimethoxyethane as

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solvent, when a mixture of ethyl 3,7,11-trimethyl-*trans*-2,6,10-dodecatrien-1-oate and ethyl 3,7,11-trimethyl-*cis*-2, *trans*-6,10-dodecatrien-1-oate was obtained in which the *trans*, *trans*-isomer predominated¹⁵. The unsaturated ester (XI) was reduced with lithium aluminium hydride affording mainly 3,7,11-trimethyl-*trans*-2,6,10-dodecatrien-1-ol (I) in 67 per cent yield.

The identity of the synthetic alcohol was established through the comparison of I.R. and N.M.R. spectra with the previously synthesised *trans*, *trans*-farnesol⁷.

Synthesis of trans-Nerolidol: Nerolidol, a sesquiterpenic tertiary alcohol, isolated from the oil of Neroli¹⁶ and from other sources¹⁷, was assigned the constitution (II) on the basis of physical and chemical properties⁸ and latter confirmed through a synthesis⁶.



Trans-nerolidol has also been synthesised by Guegon *et al.*¹⁸. The present investigations report a new synthesis of *trans*-nerolidol by the Grignard reaction of vinyl magnesium bromide on *trans*-geranylacetone (X).

The synthetic sample was confirmed through its I.R. and N.M.R. spectra.

EXPERIMENTAL*

2-Methyl-6 : 6-ethylenedioxy-heptan,-2, 3-diol (IV): 2-Methyl-6 : 6-ethylenedioxy-2-heptene (III) (40 g.) in water (2000 ml.) was cooled in an ice-salt bath (0°). To this mixture, vigorously stirred, was slowly added (2 hr.) potassium permanganate (8%; 380 ml.). The stirring was continued for a further hour, then the mixture was heated on a water-bath (100°), where the reaction mixture set to a gel prior to the precipitation of manganese dioxide.

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* M.p. and b.p. are uncorrected. I.R. spectra were determined on Perkin-Elmer Infracord with sodium chloride optics using thin liquid film and N.M.R. spectra on solutions (ca 10%) in carbon tetrachloride) using tetramethyl silane as an internal standard at 60 Mc/sec.

The mixture was filtered and the filtrate concentrated (180 ml.) under vacuum (50°). The concentrate on treatment with anhydrous potassium carbonate (65 g.) precipitated a brown oil which was partially soluble in ether (5×100 ml.). The extract was dried (anhydrous potassium carbonate), evaporated and the residue fractionated and the fraction coming at 175–80°/5 mm. was collected; yield 14 g. (29 per cent); η_D^{20} 1.4620. (Found : C, 58.45; H, 9.50. Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87%).

Infrared spectrum showed characteristic bands at 3450 cm^{-1} , 1010 cm^{-1} (—OH), and 1060 cm^{-1} (ketal).

4 : 4-Ethylenedioxy-pentanal (V) : Lead tetraacetate (45 g.) was added in small portions at 16–27° to a stirred solution of 2-methyl-6 : 6-ethylenedioxy-heptan-2, 3-diol (IV) (25 g.) in dry benzene (250 ml.). The mixture was stirred at room temperature for 2 hours and filtered, finally powdered potassium carbonate (35 g.) was added to the filtrate which was vacuum evaporated in a rotatory evaporator. The residue was carefully extracted with ether. The extract was dried with sodium sulphate, ether was removed and the residue vacuum distilled to afford 12 g. (67 per cent) of aldehyde (V); b.p. 85–90°/5 mm. (Found : C, 57.95; H, 8.01. Calc. for $C_7H_{12}O_3$: C, 58.31; H, 8.39%).

I.R. showed characteristic absorption at 2750 cm^{-1} (aldehydic C—H), 1720 cm^{-1} ($>C=O$) and 1060 cm^{-1} (ketal).

2-Methyl-6 : 6-ethylenedioxy-1-heptan-3-ol (VI) : Grignard reagent was prepared to the exclusion of moisture from dry magnesium turnings (2.2 g.), 2-bromopropene (11 g.) in anhydrous tetrahydrofuran (200 ml.). This was cooled in ice-cold water and the aldehyde (V) (11 g.) in tetrahydrofuran (20 ml.) was added dropwise with constant stirring during a period of 30 min. After the addition was complete, the contents were left overnight at room temperature and thereafter the reaction mixture was heated under reflux for about an hour to complete the reaction. The cooled contents were decomposed with saturated solution of ammonium chloride. The organic layer was separated and aqueous phase extracted with ether (3×100 ml.). The total T.H.F.-ether extract was dried over anhydrous sodium sulphate, and the solvent was removed. The residue was distilled under diminished pressure to obtain (VI), as a yellow oil, b.p. 120°/10 mm; yield 8.5 g. (59 per cent); η_D^{20} 1.4450. (Found : C, 64.38; H, 8.65. Calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%).

Infrared spectrum showed absence of absorption in the aldehydic region; characteristic peaks at 3450 cm^{-1} (—OH), 1060 cm^{-1} (ketal) 890 cm^{-1} , and 1650 cm^{-1} ($R_1R_2C=CH_2$).

2-Methyl-6 : 6-ethylenedioxy-1-hepten-3-vinyl ether (VII) : A mixture of allylic carbinol (VI) (8.4 g.), vinyl ether (V) (34 g.) and freshly-crystallised mercuric acetate (0.68 g.) was refluxed for 15 hr. The reaction mixture was cooled in ice-bath and sodium carbonate solution (10 per cent; 25 g.) was added and stirred for 30 min. The organic layer was separated, washed with water and dried over potassium carbonate. Evaporation of the solvent and chromatography of the residue on alumina (80 g.) furnished on elution with petroleum ether (40–60°), the vinyl ether (VII) which was further purified by distillation under reduced pressure to afford (VII) (4 g.) in 42 per cent yield, b.p. 103–08°/8 mm, η_D^{20} 1.4550. (Found : C, 67.35; H, 9.38. Calc. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%).

I.R. spectrum showed characteristic peaks at 1650, 1620, 1200 cm^{-1} (vinyl ether), 1060 cm^{-1} (ketal) and 890 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CH}_2$).

4-*Methyl*-8 : 8-*ethylenedioxy-trans-4-nonen-1-ol* (VIII) : Vinyl ether (VII) (4 g.) was heated for 25 minutes, under nitrogen in a fully immersed half filled sealed tube in an oil bath at 180°. After cooling, the product was distilled under reduced pressure to furnish (VIII) (3.5 g.) in 85 per cent yield; b.p. 112°/7 mm; η_D^{20} 1.4570. (Found : C, 67.36; H, 9.45. Calc. for $\text{C}_{12}\text{H}_{20}\text{O}_3$: C, 67.89; H, 9.50%).

I.R. spectrum showed characteristic peaks at 2750 cm^{-1} (aldehydic C-H), 1720 cm^{-1} ($> \text{C} = \text{O}$), 1060 cm^{-1} (ketal) and 840, 815 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CHR}_3$).

2,6-*Dimethyl*-10 : 10-*ethylenedioxy-trans-2,6-undecadiene* (IX) : The phosphorane was prepared from isopropyltriphenyl-phosphonium iodide (10.7 g.) in dimethyl sulphoxide (26 ml.), sodium hydride (1.2 g.) in dimethyl sulphoxide (13 ml.) in nitrogen atmosphere. To this was added the aldehyde (VIII) (3.5 g.) in tetrahydrofuran (10 ml.). The contents were stirred and heated for 30 min. at 50° and left overnight at room temperature. The contents were poured in crushed ice (200 ml.) and extracted with petroleum ether (40–60°; 3×100 ml.). The extract was dried (Na_2SO_4), solvent was removed and the residue chromatographed over alumina (40 g.), when elution with petroleum ether (40–60°) gave the ketal (IX) which was further purified by distillation; b.p. 112°/8 mm; yield 2.8 g. (72 %); η_D^{20} 1.4610. (Found : C, 75.11; H, 10.58. Calc. for $\text{C}_{15}\text{H}_{26}\text{O}_2$: C, 75.58; H, 11.00%).

Infrared spectrum showed the absence of any absorption in the carbonyl region; characteristic peaks at 1060 cm^{-1} (ketal) and 840,815 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CHR}_3$).

6,10-*Dimethyl-trans-5,9-undecadien-2-one* (X) : To the ketal (IX) (2.8 g.) was added acetone (56 ml.), *p*-toluenesulphonic acid (1 g.) and water (1 ml.) and the reaction mixture was stirred at room temperature for 1 hour. After removing the excess of PTS with 5 per cent sodium bicarbonate solution, the product was extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent, the residue was distilled under reduced pressure to furnish *trans*-geranylacetone (X) (1.8 g.) in 79% yield; b.p. 100°/5 mm., η_D^{20} 1.4670 (lit.¹⁹ η_D^{23} 1.4661). (Found : 79.69; H, 11.02. Calc. for $\text{C}_{13}\text{H}_{22}\text{O}$: C, 80.35; H, 11.41%).

Infrared spectrum showed characteristic peaks at 1720 cm^{-1} ($> \text{C} = \text{O}$), 840,815 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CHR}_3$).

The ketone (X) formed 2 : 4-D.N.P.H. which formed yellow needles after crystallisation from ethanol, having m.p. 57–58° (lit.¹⁹ m.p. 54–56°). (Found : N, 14.54. Calc. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_4$: N, 14.97%). The semicarbazone prepared in the usual way melted at 99–100° (lit.¹⁹ m.p. 96–97°). (Found : N, 16.25. Calc. for $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}$: N, 16.73%).

Ethyl 3,7,11-*trimethyl-trans-2,6,10-dodecatrien-1-olate* (XI) : A slurry of sodium hydride (0.38 g.) was placed in 1,2-dimethoxyethane (50 ml.) and ethyl diethylphosphonoacetate (2.6 g.) was added dropwise at room temperature. After the addition, the solution was

stirred until the evolution of gas had ceased. To the resulting yellow solution was then added the ketone (IX) (2 g.) slowly and below 10° . After the addition, the solution was further stirred for 3 hr. and then refluxed for 30 min. The product was extracted with ether and dried (Na_2SO_4). The solvent was removed and the residue on distillation under reduced pressure afforded 1.6 g. (76 per cent) of ethyl 3,7,11-trimethyl-*trans*-2,6,10-dodecatrien-1-oate and *cis*-2, *trans*-6 isomers which showed two spots on t.l.c. (*n*-hexane : benzene :: 1 : 1); b.p. $140-45^\circ/5$ mm. η_D^{20} 1.4840. (Found : C, 76.86; H, 10.38. Calc. for $\text{C}_{17}\text{H}_{28}\text{O}_2$: C, 77.22; H, 10.67%).

I.R. spectrum showed characteristic peaks at 1720 cm^{-1} ($> \text{C} = \text{O}$), 1650 , 970 cm^{-1} (*trans* double bond) and 840 , 815 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CHR}_3$).

3,7,11-Trimethyl-*trans*-2,6,10-dodecatrien-1-ol (I) : To a fine suspension of lithium aluminium hydride (0.15 g.) in anhydrous ether (50 ml.) was added dropwise stirring a solution of the ester (XI) (1.6 g.) in ether (15 ml.) so as to keep the ether at a gentle reflux. The contents were further stirred for three hours at room temperature and then the metal-complex was decomposed with saturated sodium sulphate solution. The organic layer was taken up in ether and dried (Na_2SO_4). Evaporation of the solvent followed by vacuum distillation afforded mainly *trans*, *trans*-farnesol (I) (1.10 g.) in 67 per cent yield; b.p. $152^\circ/5$ mm.; η_D^{24} 1.4860 (lit.¹² η_D^{25} 1.4872). (Found : C, 80.76; H, 11.33. Calc. for $\text{C}_{15}\text{H}_{26}\text{O}$: C, 81.08; H, 11.71%).

I.R. spectrum showed bands at 3450, 2950, 1650, 1400, 1350, 1010, 1000, 970, 840 and 815 cm^{-1} identical to those given in lit.⁷ from *trans*, *trans*-farnesol at 3450, 2950, 1650, 1400, 1350, 1010, 960, 835 and 815 cm^{-1} .

The synthetic alcohol was further confirmed by its N.M.R. spectrum which showed signals at 8.34 (3H, one allylic methyl), 8.41 (6H, two allylic methyls), 7.91 (3H, C(2)- CH_3), 5.9, 6.0 (2H, $\text{CH}_2\text{-OH}$), 4.6, 4.7, 4.9 (3H, vinylic protons) comparable to those reported in lit.⁷ at 8.34, 8.40, 7.9, 6.0, 4.6, 4.7 and 4.9.

3,7,11-Trimethyl-*trans*-1,6,10-dodecatrien-3-ol (II) : To the Grignard reagent prepared from vinyl bromide (1 g.), magnesium (0.12 g.) in dry tetrahydrofuran (100 ml.) was added dropwise the ketone (X) (1 g.) in tetrahydrofuran (10 ml.) in cold. After standing overnight, the reaction mixture was decomposed with saturated solution of ammonium chloride and worked up in the manner of (VI) to furnish *trans*-nerolidol (II; 0.6 g.) (53 per cent); (Found : C, 80.66; H, 11.25. Calc. for $\text{C}_{15}\text{H}_{26}\text{O}$: C, 81.08; H, 11.71%).

The identity of the synthetic compound was established through its I.R. absorption spectrum which showed peaks at 3450 , 1140 cm^{-1} ($-\text{OH}$), 1450 , 1375 cm^{-1} ($\text{C}-\text{CH}_3$) and 1650 , 890 cm^{-1} ($\text{R}_1\text{R}_2\text{C} = \text{CH}_2$).

It was further confirmed by its N.M.R. spectrum which showed characteristic signals at 8.78 (3H, C(3)- CH_3), 8.41 (6H, two vinylic methyls), 8.34 (3H, one vinylic methyl), 4.88 (2H, vinylic protons), 5.0 (quartet) (1H, C(1)- H_c), 4.81 (quartet), (1H, C(1)- H_b) and 4.12 (quartet) (1H, C(2)- H_a).

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